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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/536,560	12/20/2005	Itzhak Bentwich	050992.0300PCUS	9481

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EXAMINER	
SHIN, DANA H	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/536,560	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,6,8,9,12,13 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,8,9,12,13 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below.

CFR §1.821(d) reads as follows:

> Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

Pages 36, 37, 41, and 42 of the instant specification as well as Figures 14-16 contains nucleic acid sequences which are not preceded by "SEQ ID NO:". Applicants are reminded that either the brief description of drawings for Figures 14-16 or Figures themselves should make a reference to the sequences by use of the sequence identifiers in accordance with CFR §1.821 through 1.825. Applicants are also reminded that the nucleic acid sequences disclosed in the application must be entered in the paper copy of sequence listing as well as CRF. See Notice to Comply. Any response to this action must correct this deficiency, as this requirement will not be held in abeyance.

Status of Claims

Claims 2, 4-5, 7, 10-11, 14-17, and 19-20 have been cancelled. Claims 1, 3, 6, 8-9, 12-13, and 18 are pending and currently under examination on the merits.

Information Disclosure Statement

The listing of references in the Search Report is not considered to be an information disclosure statement (IDS) complying with 37 CFR 1.98. 37 CFR 1.98(a)(2) requires a legible copy of: (1) each foreign patent; (2) each publication or that portion which caused it to be listed; (3) for each cited pending U.S. application, the application specification including claims, and any drawing of the application, or that portion of the application which caused it to be listed including any claims directed to that portion, unless the cited pending U.S. application is stored in the Image File Wrapper (IFW) system; and (4) all other information, or that portion which caused it to be listed. In addition, each IDS must include a list of all patents, publications, applications, or other information submitted for consideration by the Office (see 37 CFR 1.98(a)(1) and (b)), and MPEP § 609.04(a), subsection I. states, "the list ... must be submitted on a separate paper." Therefore, the references cited in the Search Report have not been considered. Applicant is advised that the date of submission of any item of information or any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the IDS, including all "statement" requirements of 37 CFR 1.97(e). See MPEP § 609.05(a).

Specification

The disclosure is objected to because of the following informalities: The title of the instant application as well as the abstract contain the term, "novel". The title as well as the abstract of a patent application should be descriptive of the claimed subject matter, which is presumed to be novel. See M.P.E.P. §606. Accordingly, the term "novel" is not descriptive of the claimed subject matter in the instant case because it is obvious that claimed invention be novel.

Appropriate correction is required.

The disclosure is objected for containing sequence non-compliance subject matter in Figures 14-16 and at least pages 36, 37, 41, and 42 in the specification. See Notice to Comply.

Applicant is reminded of the proper language and format for an abstract of the disclosure. The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. The form and legal phraseology often used in patent claims, such as "thereof" should be avoided. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of claims 9 and 18 embraces only *in vivo* methods because the recited methods are performed in a host.

The instant specification provides only *in vitro* infection examples wherein HeLa cells are infected with miRNAs. As claimed, the methods of claims 9 and 18 must inhibit translation of a target gene in a host or treat viral infection in a host comprising introducing miRNAs. The state of gene therapy art was far from being predictable or routine at the time the instant application was filed. Even a post-dated reference warns against extremely low success of the introduction of DNA-based drugs for therapeutic use. See for example, Patil et al. (*American*

Association of Pharmaceutical Scientists Journal, 2005, 7(1):E61-E77) that teaches the following on page E62:

> "Despite many favorable characteristics and signs of possible clinical victories (see Table 1), the introduction of DNA-based drugs for human use can be best described as limited, with rare successes. The inertia in the development of these drugs can be attributed, in part, to their poor cellular uptake profile *in vivo.* The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics....The resulting random delivery profile of DNA-based drugs is further complicated by a lack of *in vivo/in vitro* correlation of their pharmacological outcomes."

In light of the above, it would have been unpredictable whether the claimed invention would have elicited successful inhibition of viral infection/expression, had the vector comprising a miRNA targeted to a viral sequence been administered to a host *in vivo* at the time the inventions of claims 9 and 18 were made, particularly since no positive correlation between *in vivo/in vitro* effect of miRNAs was established by the instant disclosure. Moreover, the instantly claimed invention would require undue experimentation as the reference of Patil et al. teaches that a clinical application of DNA-based drugs, such as shRNA or miRNA of the instant application, requires careful series of trial and error tests for ensured success of bioavailability and pharmacokinetics of the DNA-based drugs due to "unpredictable pharmacokinetics" of internalized DNA-based drugs (page E62). In view of the foregoing, the instant disclosure does not provide any guidance required to overcome the art-recognized unpredictability of using DNA-based drugs in therapeutic applications in a host *in vivo.* Taken together, undue experimentation would have been needed to use the claimed invention based on the content of the disclosure (i.e., amount of direction and existence of working examples provided by the inventor) and the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art. In view of all these factors and the totality of the teachings that the

activity of DNA-based drugs are unpredictable *in vivo*, undue experimentation would be required of the skilled artisan to practice the instantly claimed invention, thus claims 9 and 18 are not enabled.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6, 8-9, 12-13, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 6, 8-9, 12-13, and 18 depend from claim 1.

Claim 1, lines 8-9 recite "a partial inversed-reversed sequence of a sequence". Since the term "inversed-reversed sequence" is not defined either by the claim or the specification, one of ordinary skill in the art would not be reasonably apprised of the structure of the claimed isolated DNA, thereby rendering claim 1 and its dependent claims indefinite.

For examination purpose, the claim language reciting "a partial inversed-reversed sequence of a sequence" will be interpreted as a complementary sequence based on the content of the disclosure of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 6, 8, and 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Cullen et al. (US 2004/0053411 A1).

The claims are drawn to an isolated viral DNA encoding RNA comprising about 50-120 nucleotides, of which about 18-24 nucleotides are partially complementary and targets at least one host gene, wherein the RNA modulates expression of the gene, a UTR is targeted, a vector comprising DNA, and a probe comprising a sequence complementary to any portion of the RNA and a method of detecting miRNA expression with the probe.

Cullen et al. teach an isolated DNA encoding an miRNA that targets conserved sequences (e.g., packaging sequences or regulatory elements) in viruses of hepatitis C virus, papilloma virus, and HIV (paragraphs 0026-0028). They specifically teach a mir-30 precursor and a vector encoding mir-30, which inhibits endogenous SV40 T antigen expression in cells *in vitro* (paragraphs 0002-0009, 0019-0028; Figures 1-5). They teach that mir-30 is encoded by 70 nucleotide mir-30 precursor and that transfection of a vector encoding the entire mir-30 RNA precursor reduces the level of HIV *tat* (paragraphs 0049-0055). They teach primers/probes that detect the presence of mir-30 miRNA (paragraphs 0036, 0044-0046). They teach that microRNA precursors have about 40-100 nucleotides, preferably, about 50-75 nucleotides, of which about 20-30 nucleotides form partial, self-complementary strands and that miRNAs hybridize with complementary sequences in the 3' UTR (paragraph 0022, 0048). Accordingly, all the structural limitations of the claims are taught by Cullen et al.

Claims 1, 3, 8, and 12-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Rossi et al. (US 2005/0074887 A1).

The claims are described above.

Rossi et al. teach a DNA construct encoding miRNA, shRNA, or other siRNA precursor that is targeted to the HIV-1 *rev* sequence and inhibits the expression of HIV-1 (paragraphs 0014-0015, 0034-0038). They teach a DNA probe that is complementary to the miRNA target sequence and a method of detecting the miRNA with the probe (paragraph 0032). Accordingly, all the structural limitations of the claims are taught by Rossi et al.

Claims 1, 3, 6, 8-9, 12-13, and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen et al. (US 2004/0242518 A1).

Claims 1, 3, 6, 8, and 12-13 are described above.

Claims 9 and 18 are drawn to methods of inhibiting viral translation and infection in a host comprising introducing a vector containing a viral DNA encoding RNA.

Chen et al. teach shRNAs and vectors encoding shRNA precursors that target influenza virus sequence (paragraphs 0007-0009, 0089, 0091). They teach partially complementary double-stranded hairpin RNA precursor structure, which inhibit influenza virus replication (Figures 20-25; Example 11). They teach that certain double-stranded RNAs hybridize to a target site that includes 3' UTR sequences and they may tolerate a large number of mismatches in the RNA/template duplex (paragraphs 0147-0148). They teach that the amount of the target transcript can be assessed by Northern blots, RT-PCR, and PCR, all of which use DNA probes (paragraph 0179). They teach that administration of siRNAs targeted to influenza virus NP or PA

transcripts inhibit production of influenza virus in mice (Figures 22-23, 25-26; Examples 12, 14). Accordingly, all the claim limitations are taught by Chen et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 6, 8, and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jacque et al. (*Nature,* 2002, 418:435-437) in view of Hutvagner (*Science,* 2002, 297:2056-2060) and Paillart et al. (*The Journal of Biological Chemistry,* 2002, 277:5995-6004).

The claims are described above.

Jacque et al. teach synthetic double-stranded RNAs or plasmid-derived siRNAs targeted to various regions of HIV-1 genome including the viral long terminal repeat, *vif,* and *nef.* They teach that siRNA duplexes reduce virus production by 30 to 50 fold when transfected into cells (page 435; Figure 1). They also teach that the HIV-1 siRNA duplexes markedly reduce the level of HIV RNA in cells and interfere with the HIV replication (pages 436-437). They teach that expression of siRNAs from plasmid vectors offers several advantages over synthetic siRNAs, such as stable selection markers and inducible promoters (page 4367). They teach that siRNAs expressed by plasmid vectors have hairpin structures with a 19-bp self-complementary stem region and non-base paired loops of 3, 5, and 7 nucleotides (page 437; Figure 3). They teach

PCR primers and oligonucleotide probe for real-time PCR as well as RT-PCR primers (pages 435-438). Jacque et al. do not teach the HIV-1 target sequence is in the untranslated region nor do they teach general structural features of miRNAs.

Hutvagner et al. teach that Dicer enzyme produces microRNAs (miRNAs) from about 70 nucleoitde hairpin precursor (page 2056). They teach that miRNAs hybridize with target mRNAs that contain partially complementary sequences and repress mRNA translation without altering mRNA stability (page 2056; Figure 4). They teach that miRNAs together with siRNAs form a miRNP/RISC complex to mediate translational repression (via stRNA) and target cleavage (via siRNA), respectively and that miRNAs can function in the RNAi pathway (pages 2057-2059; Figure 4).

Paillart et al. teach that the 5'-untranslated region of HIV-1 RNA contains multiple regulatory regions that control distinct steps of the viral replication cycle such as transcription, reverse transcription, genomic RNA dimerization, splicing, and packaging (page 5995; Figure 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art to modify the HIV-1 shRNA molecules of Jacque et al. in view of Hutvagner et al. and Paillart et al. One of ordinary skill in the art would have been motivated to do so because Hutvagner et al. expressly teach the advantage of miRNAs over siRNAs, which is that miRNAs hybridize with target mRNAs that contain partially complementary sequences and repress mRNA translation without altering mRNA stability (page 2056), and because Paillart et al. expressly teach that the 5' UTR of HIV-1 RNA contains multiple essential regulatory regions that are critical for HIV replication. Since the HIV-1 shRNA molecules of Jacque et al. successfully reduce the level of HIV in infected cells, the

skilled artisan would have had a reasonable expectation of success in making miRNA molecules targeted to 5'UTR region of the HIV-1 RNA that modulate the HIV-1 expression. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 6, 8, and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-38 of copending Application No. 10/709,572. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in claims 25-38 of copending Application No. 10/709,572 is a species of the broadly claimed invention in the instant case, as evidenced by the fact that claimed SEQ ID NOs: 45 and 159 are HIV target sequences (see claims 27 and 31 and Table on page 119 of the specification). Therefore, the examined application claims are anticipated by and would have been obvious over, the reference claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 6, 8, and 12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-34 of copending Application No. 10/709,739. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in claims 23-34 of copending Application No. 10/709,739 is a species of the broadly claimed invention in the

instant case, as evidenced by the fact that claimed SEQ ID NOs: 117937 and 118171 are human herpes virus target sequences. Therefore, the examined application claims are anticipated by and would have been obvious over, the reference claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 3, 6, 8-9, 12-13, and 18 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 12-16 of copending Application No. 11/511,035. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in claims 1-4 and 12-16 of copending Application No. 11/511,035 is a species of the broadly claimed invention in the instant case. Therefore, the examined application claims are anticipated by and would have been obvious over, the reference claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 37 CFR §1.821(g). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. §§1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. §§1.821-1.825. Applicants attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. §1.821(c).
- [ ] 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. §1.821(e).
- [ ] 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. §1.822 and/or 1.823, as indicated on the attached copy of the marked-up Raw Sequence Listing.
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. §1.825(d).
- [ ] 6. The paper copy of the Sequence Listing is not the same as the computer readable from of the Sequence Listing as required by 37 C.F.R. §1.821(e).
- [ ] 7. Other:

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the Sequence Listing. (If the unidentified sequences are not provided on the CRF)
- [X] An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification. (If the unidentified sequences are not provided in the paper copy)
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). (If a new paper and/or CRF are required)

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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